Selective Aerobic Oxidation of Alcohols with a Combination of a Polyoxometalate and Nitroxyl Radical as Catalysts

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Introduction

The discovery of new environmentally friendly methods for selective catalytic oxidation of alcohol substrates to aldehyde and ketones is an important goal in the development of modern methods for chemical synthesis.[1] In this context, of special significance is the use of intrinsically non-waste-producing oxidants such as molecular oxygen from air and hydrogen peroxide. It has been shown in the past that stable nitroxyl radicals such as 2,2,6,6-tetramethylpiperidine-1-oxy (TEMPO) is able to mediate the oxidation of primary alcohols to aldehydes with a variety of terminal oxidants.[2] Especially common is the use of hypochlorite,[3] but the use of electrocatalytic conditions,[4] peracetic acid together with a catalytic amount of bromide,[5] *m*-chloroperbenzoic acid,[6] bromite,[7] persulfate,[8] and hydrogen peroxide together with hydrogen bromide and methylrhenium trioxide as catalyst have also been reported.[9] The use of these nitroxyl reaction systems has one or more disadvantages including a high price of oxidant, formation of considerable amounts of organic waste, and the use of halide (chloride and/or bromide)-containing oxidants which in turn form nondesirable halide-containing wastes. To obviate these disadvantages, molecular oxygen can also as be used as terminal oxidant in the presence of cupric ion catalysts,[10] a ruthenium catalyst, $RuCl_2(PPh_3)_3$,[11] or enzymes with or without metal complexes.[12] These methods have the advantage of being intrinsically waste-free synthetic systems as concerns the oxidant. However, they have other disadvantages. The copper-based method is largely ineffective for simple (nonallylic or nonbenzylic) aliphatic especially secondary alcohols. In addition, relatively high catalytic loads, usually at least 10 mol % each of TEMPO and cupric ion are needed. The ruthenium-based system overcomes the disadvantage of the lack of reactivity for simple aliphatic alcohols, but it requires an expensive noble metal and preferably an intrinsically oxidatively unstable triphenylphosphine ligand, which has to be present in order to obtain appreciable catalyst activity. The enzyme-based method affords only low to modest conversions after long reaction times, and the rate of these enzymatically catalyzed oxidation reactions cannot be increased by significantly increasing the temperature because of the thermal lability of the enzymes.

Results and Discussion

In this present communication we describe the highly selective and active aerobic oxidation of alcohols in the combined presence of a nitroxyl radical, TEMPO, and a polyoxometalate, $H_5PV_2Mo_{10}O_{40}$, as cocatalysts. This specific polyoxometalate has been shown to have catalytic activity in a myriad of applications[13] with, however, only limited reactivity for alcohol oxidation.[14] Typically, reactions were carried out in solution by mixing the alcohol substrate with catalytic amounts of $H_5PV_2Mo_{10}O_{40} \times 34H_2O$, and TEMPO, in acetone under 2 atm O_2 in a 25 mL glass pressure tube. The results, Table 1, showed high conversion of the alcohol substrate. In all cases, ketones or aldehydes were the only detected reaction products in the oxidation of secondary and primary alcohols, respectively. Clearly the method is universal for the oxidation of benzylic, allylic, secondary, and primary alcohols to their respective carbonyl compounds without over-oxidation. The rates of oxidation of the representative benzylic, allylic, secondary, and primary alcohols were studied in order to distinguish between the reactivity of the different alcohol types using benzyl alcohol, *cis*-2-hexen-1-ol, 2-octanol, and 1-octanol as substrates. Oxidation of benzyl alcohol and *cis*-2-hexen-1-ol (1 M alcohol (ROH), 0.01 M $H_5PV_2Mo_{10}O_{40}$, 0.03 M TEMPO, 2 atm O_2) proceeded already at 25 °C with rates of $-d[ROH]/dt = 8.5 \times 10^{-4}$ M/min and 6.3×10^{-4} M/min, respectively. For 2-octanol and 1-octanol, similar (slightly higher) rates were observed only at 100 °C, $-d[ROH]/dt = 2.8 \times 10^{-3}$ M/min and 2.1×10^{-3} M/min, respectively. Clearly, the rates of oxidation of alcohols are benzylic ~ allylic > secondary ~ primary. This reactivity profile, especially the observation that the rate of oxidation of 2-octanol is similar to that of 1-octanol, is typical of such alcohol oxidation reactions under acidic conditions.[15] A further full study of the reaction kinetics using benzyl

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Table 1. Aerobic Oxidation of Alcohols Catalyzed by TEMPO/$H_5PV_2Mo_{10}O_{40}$

alcohol	product	conversion, mol %	reaction time, h
1-octanol	1-octanal	98.4	18
1-octanol (no TEMPO)	1-octanal	0.2	18
2-octanol	2-octanone	95.7	18
3-octanol	3-octanone	94.3	18
cyclooctanol	cyclooctanone	95.5	18
cyclohexanol	cyclohexanone	96.1	18
benzyl alcohol	benzaldehyde	99.6	6
benzyl alcohol (no TEMPO)	benzaldehyde	8.4	6
1-phenylethanol	acetophenone	98.3	6
4-methylbenzyl alcohol	4-methylbenzaldehyde	>99.9	6
4-nitrobenzyl alcohol	4-nitrobenzaldehyde	93.1	6
4-chlorobenzyl alcohol	4-chlorobenzaldehyde	98.7	6
cis-2-hexen-1-ol	2-hexenal	>99.9	10
cis-2-hexen-1-ol (no TEMPO)	2-hexenal	1.1	10
trans-2-hexen-1-ol	2-hexenal	>99.9	10

[a] Reaction conditions: In a 25 mL glass pressure tube were loaded 1 mmol of alcohol, 0.01 of mmol $H_5[PMo_{10}V_2O_{40}]$, 0.03 mmol of TEMPO, and 0.15 mL of acetone. Oxygen was added to a pressure of 2 atm, and the pressure tube was placed in an oil bath thermostated at 100 °C. After the given time period, the glass pressure tube was removed from the oil bath, cooled to room temperature, and then analyzed by gas chromatography using an Hewlett-Packard 6980 GC apparatus equipped with a Restek Rtx-5MS column (30 m × 0.32 mm with a 0.25 μm coating).

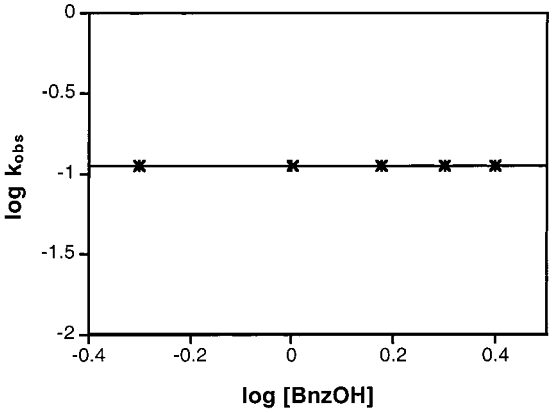


Figure 1. Dependence on the concentration of benzyl alcohol. Reaction conditions: 0.5–2.5 M benzyl alcohol, 0.03 M TEMPO, 0.01 M $H_5PV_2Mo_{10}O_{40}$ in 1 mL acetone at 25 °C under 1 atm O_2.

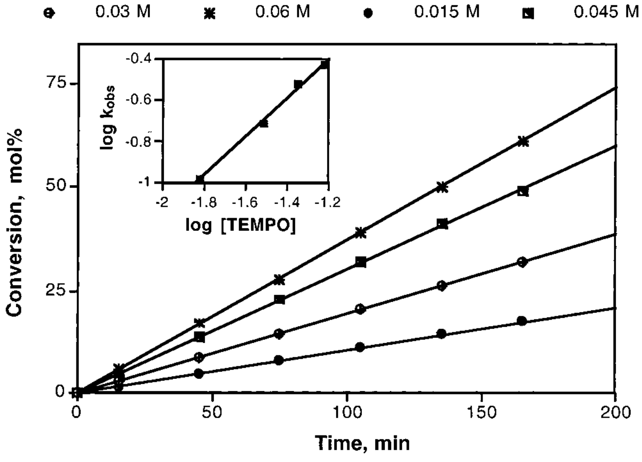


Figure 2. Dependence on the concentration of TEMPO. Reaction conditions: 1 M benzyl alcohol, 0.015–0.06 M TEMPO, 0.01 M $H_5PV_2Mo_{10}O_{40}$ in 1 mL of acetone at 25 °C under 1 atm O_2. Slope or reaction order in TEMPO from the inserted graph = 0.94, $r^2 = 0.99$.

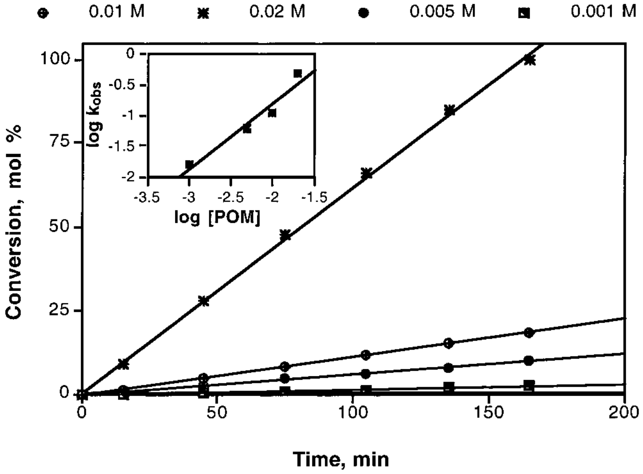


Figure 3. Dependence on the concentration of polyoxometalate. Reaction conditions: 1 M benzyl alcohol, 0.03 M TEMPO, 0.001–0.02 M $H_5PV_2Mo_{10}O_{40}$ in 1 mL of acetone at 25 °C under 1 atm O_2. Slope or reaction order in the polyxoxmetalate for the inserted graph = 1.07, $r^2 = 0.95$.

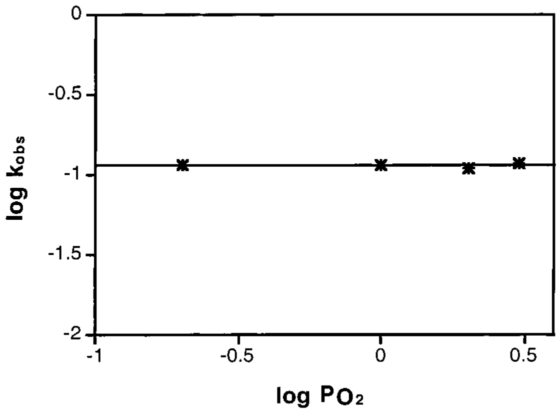
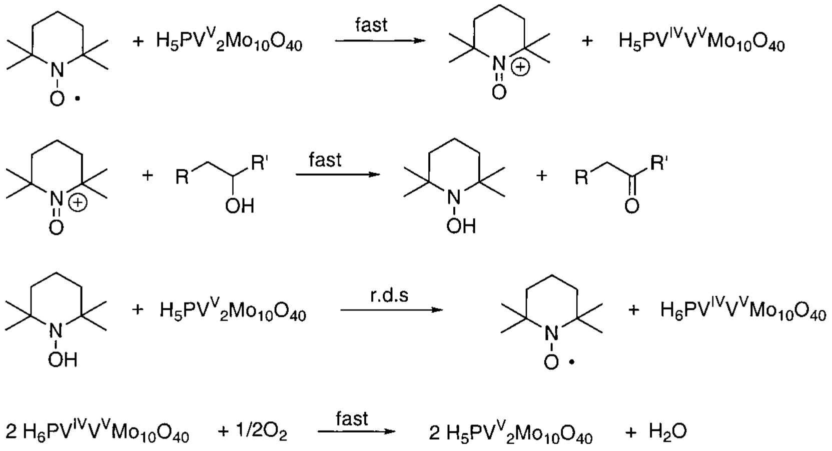


Figure 4. Dependence on the pressure of oxygen. Reaction conditions: 1 M benzyl alcohol, 0.03 M TEMPO, 0.01 M $H_5PV_2Mo_{10}O_{40}$ in 1 mL of acetone at 25 °C under 1 atm O_2.

alcohol as a model substrate revealed rather surprisingly that the reaction was not dependent on its concentration, Figure 1. Furthermore, a competitive kinetic isotope experiment using a 1:1 mixture of benzyl alcohol and benzyl alcohol-d_7 (0.5 M BnzOH, 0.5 M BznOH-d_7, 0.01 M $H_5PV_2Mo_{10}O_{40}$, 0.03 M TEMPO, 2 atm O_2, 25 °C) showed no isotope effect ($k_H/k_D = 1 \pm 0.02$). Also, a kinetic isotope experiment carried out for separate oxidation of

Scheme 1



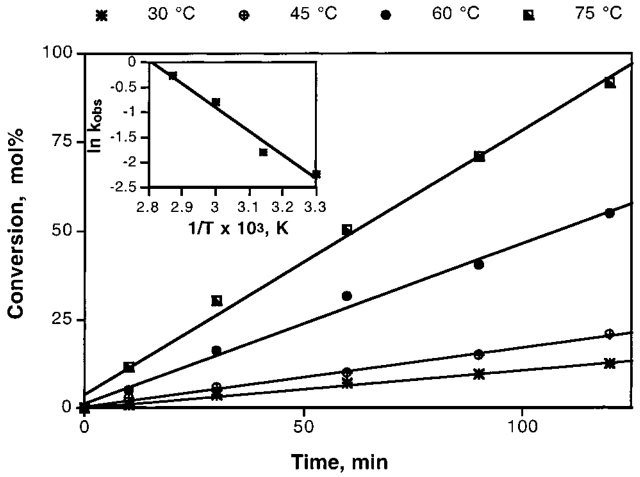


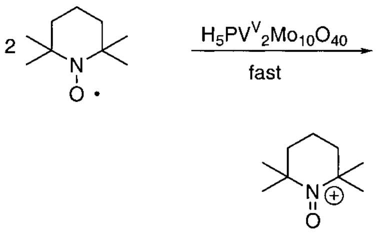
Figure 5. Dependence on the temperature reaction conditions: 1 M benzyl alcohol, 0.03 M TEMPO, 0.01 M $H_5PV_2Mo_{10}O_{40}$ in 1 mL of acetone at 25−75 °C under 1 atm O_2.

benzyl alcohol and benzyl alcohol-d_7 showed the same rate (±5%) of oxidation for both substrates. For the other reaction components, it was found using van't Hoff plots that the reaction was first order each in the concentration of $H_5PV_2Mo_{10}O_{40}$ and TEMPO, but zero order in molecular oxygen, Figures 2−4. The fact that the reaction is not dependent on the oxygen pressure means that it might be equally efficient in oxygen or air. A study of the rate as a function of the temperature, Figure 5, gave activation parameters, $E_a = 9.54$ kcal mol^{-1}, $\Delta H^{\ddagger}_{25\ °C} = 8.95$ kcal mol^{-1} and $\Delta S^{\ddagger}_{25\ °C} = -31.44$ cal mol^{-1} K^{-1}. The $\Delta S^{\ddagger}_{25\ °C}$ value is consistent with a bimolecular transition state in the rate-determining step. The rate equation may be summarized as follows, eq 1

$$-\frac{d[BnzOH]}{dt} = k_{obs}[TEMPO][H_5PV_2Mo_{10}O_{40}];\ k_{obs} = 7.7 \times 10^6\ e^{-9540/RT} = \frac{kT}{h}9e^{-31.44/R}(e^{-8950/RT}) \quad (1)$$

Other valuable observations concerning this reaction are to be noted. When the $H_5PV_2Mo_{10}O_{40}^-$ polyoxometalate and TEMPO are mixed in acetone, the solution immediately turns green, indicating that the polyoxometalate is reduced and the TEMPO is oxidized. Thus, an ESR spectrum of a mixture of 1/1TEMPO/$H_5PV_2Mo_{10}O_{40}$ reveals no typical spectrum for the nitroxyl radical, but does show the typical spectrum for reduced $H_5PV_2Mo_{10}O_{40}$. Second, an acidic but nonoxidizing polyoxometalate such as $H_3PW_{12}O_{40}$ does not significantly oxidize benzyl alcohol under conditions where both TEMPO as well as $H_3PW_{12}O_{40}$ are used catalytically (3 and 1 mol %, respectively). These two observations supported by the kinetic studies lead us to suggest the following mechanism for aerobic TEMPO/$H_5PV_2Mo_{10}O_{40}$ catalyzed oxidation of alcohols to the respective carbonyl compound, Scheme 1. The reaction sequence is initiated by oxidation of the nitroxyl radical to the nitrosium cation, the active alcohol oxidizing species. There is probably some ion pair formation since similar to all quaternary ammonium cations the nitrosium ion tends to exchange with the proton of the polyoxometalate. In the absence of alcohol some green precipitate is formed. The nitrosium cation or the nitrosium cation−polyoxometalate ion pair then oxidizes the alcohol. This step is apparently relatively fast since for benzyl alcohol the reaction was zero order in the alcohol and there was no kinetic isotope effect. Since the kinetic studies show that the reaction is first-order both in the TEMPO precursor and the polyoxometalate, we postulate that in the rate-determining step the hydroxylamine is reoxidized to TEMPO by $H_5PV_2Mo_{10}O_{40}$.[16] The oxidized form of the polyoxometalate is regenerated by molecular oxygen in a further, relatively fast, step.[17]

Scheme 2



Since the polyoxometalate is also very acidic, some nitrosium species may be formed by an acid-catalyzed disproportionation of the nitroxyl radical to the nitrosium cation and hydroxylamine, Scheme 2.[18]

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[16] The mechanism is supported by the kinetic studies carried out on the oxidation of benzyl alcohol. It is reasonable that for the more difficult to oxidize substrates such as 1-octanol, the rate-determining step would be the alcohol oxidation; in this case the reoxidation of the hyrdoxylamine to the nitroxyl radical would be relatively fast.

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In fact, a quantitative ESR experiment revealed that after mixing equivalent amounts of TEMPO and an acidic but nonoxidizing polyoxometalate, $H_3PW_{12}O_{40}$, approximately 80% of the TEMPO disproportionated within 10 min. Therefore, it is reasonable that acid catalysis may contribute to the formation of the nitrosium cation.

Experimental Section

The $H_5PV_2Mo_{10}O_{40} \times 34H_2O$ polyoxometalate was prepared using a known literature method.[19] Thermogravimetric analysis (Mettler 50) indicated 34 water molecules per polyoxometalate, and the elemental analysis was as follows: found (calculated) % P 1.31 (1.34), V 4.38 (4.41), Mo 41.32 (41.56). IR 1057, 960, 865, and 774 cm^{-1}. ^{31}P NMR (CD_3COCD_3, 85% H_3PO_4 external standard) −3.96 (6), −3.42 (1), −3.37 (4), −3.31 (2), and −3.22 (2) ppm (area of peak). Reactions were carried out in 15 mL glass pressure tubes. Typically, appropriate amounts of the substrate (all highest purity commercial products) and polyoxometalate catalyst were dissolved in reaction solvent. Oxygen was introduced to the pressure tube by four consecutive pump−thaw cycles on a Schlenk line. Conversions of the organic substrate after the appropriate time period as given in the table and figure captions were measured by GLC using a 5% phenymethylsilicone (30 m, 0.32 mm ID, 0.25 μm coating) column.

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